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Original article

Prevalence of subclinical coronary artery disease in ischemic stroke patients

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ABSTRACT

Background: Recently, ischemic stroke has emerged as a new coronary artery disease (CAD) risk equivalent. Our purpose is to study the prevalence of CAD in ischemic stroke patients compared with that in non-stroke patients.

Methods and results: We measured coronary calcium score (CCS) in 151 ischemic stroke patients without known CAD (stroke group) and compared it with 151 age- and sex-matched non-stroke patients (control group). CCS was significantly higher in the stroke group than in the control group (stroke group, median: 64, interquartile range: 3–382 vs. control group, median: 3, interquartile range: 0–65, $p < 0.0001$). High-risk CAD, defined as a CCS $\geq$ 400, was detected in 24.5% of the stroke group compared with 9.3% of the control group ($p < 0.0001$). Agreement between the Framingham risk score and CCS was found in only 62 patients (41.1%). In a multiple logistic regression analysis, age [hazard ratio (HR) 1.09, 95% confidence interval (CI) 1.03–1.14], diabetes (HR 2.97, 95%CI 1.52–5.78), stroke (HR 3.85, 95%CI 1.89–7.81), and male sex (HR 4.41, 95%CI 1.82–0.75) were significantly associated with high-risk CAD ($p < 0.001$).

Conclusions: Our results show that the prevalence of subclinical CAD in ischemic stroke patients was high, and that a quarter of them had high-risk CAD. Age, diabetes, stroke, and male sex were independent predictors of high-risk CAD.

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in both developing and developed countries [1]. Current guidelines for the primary and secondary prevention of cardiovascular disease, such as the American Heart Association guidelines and the National Cholesterol Education Program Adult Treatment Panel III guideline, define patients with coronary heart disease (CHD) risk equivalents as those who are at the same elevated risk as patients with ischemic heart disease [1–3]. CHD risk equivalents include diabetes mellitus, peripheral artery disease, carotid artery disease, and abdominal aortic aneurysm.

Recently, ischemic stroke without carotid artery disease has emerged as a new CHD risk equivalent. Dhamoon and Elkind [4], in a review of evidence from hospital- and population-based studies, proposed that stroke could be designated as a CHD risk equivalent, and that could be included in the outcome cluster for absolute estimation of risks in primary and secondary prevention [4]. More recently an American Heart Association/American Stroke Association Scientific Statement was released [5]. This statement concludes that patients with atherosclerotic stroke should be included among those deemed to be at high risk (≥20% over 10 years) of further atherosclerotic coronary events.

Several studies have investigated the prevalence of significant CAD in ischemic stroke or transient ischemic attack patients [6–8]. However, few studies measured coronary calcium score (CCS), which is a powerful predictor of cardiac events in stroke patients [9–11]. One study measured CCS and carotid intima–media thickness in community-dwelling men and women with a mean age of 80 years and found that CCS and carotid intima–media thickness can similarly predict total cardiovascular events, myocardial infarction, and stroke [12]. Furthermore, no study has compared the prevalence of CAD in stroke patients with that in

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non-stroke patients. We therefore measured CCS in ischemic stroke patients without known CAD and compared the results with those of age- and sex-matched non-stroke patients.

Methods

Patients

From September 2011 through September 2012, 184 patients with acute ischemic stroke were admitted to our hospital. The diagnosis of ischemic stroke was made according to the National Institute of Neurological Disorders and Stroke criteria [13]. We measured CCS of ischemic stroke patients. The following patients were excluded: (1) patients who died; (2) patients with disabling stroke (modified Rankin scale score $\geqq 3$); (3) patients older than 80 years; (4) patients with cardioembolic stroke; (5) patients with symptomatic carotid artery disease, defined as stenosis $\geq$50% by Duplex ultrasonography; (6) patients with known CAD; (7) patients with atrial fibrillation; or (8) patients who refused CCS measurement. Thus, 151 patients underwent CCS measurement (stroke group). Sixty-four patients had lacunar infarcts, 81 patients had atherothrombotic infarcts, and 6 patients had infarcts of an unknown type.

Over the same period, 407 non-stroke patients with coronary risk factors but without known CAD underwent CCS measurement. For inclusion in the control group, we randomly selected 151 patients from this group who were matched for age and sex with the above 151 ischemic stroke patients.

Framingham risk score

We calculated Framingham risk score (FRS) in each patient in the stroke group [14]. The 10-year risk of myocardial infarction and cardiac death was calculated using this score. Risk was defined as follows: low, less than 10%; intermediate, between 10% and 20%; or high, greater than 20%.

64-Multidetector computed tomography

All patients were scanned with a 64-multidetector computed tomography (64-MDCT) system (SOMATOM Sensation 64 Cardiac; Siemens Medical Solutions, Erlangen, Germany). A native scan without contrast dye was performed to determine the total calcium burden of the coronary tree (sequential scan with 32-mm $\times$ 0.6-mm collimation, tube current 60 mA s at 120 kV). A total of 64 overlapping 3.0-mm slices per rotation were acquired using a focal spot, periodically moving longitudinally (z-flying focal spot). The tube current was modulated according to the electrocardiogram (ECG), with a maximum current of 200 mA s during a period of approximately 330 ms centered at 375 ms before the next R-wave, and reduced by 80% during the remaining cardiac cycle (care dose system).

64-MDCT image interpretation

CT data sets were transferred to an offline workstation (Aquarius NetStation, Terarecon Inc., San Maeteo, CA, USA) for image analysis. One physician measured CCS in the right coronary artery, left main trunk, left anterior descending coronary artery, and left circumflex coronary artery, then calculated the total CCS with dedicated software. The results were expressed as Agatston score [15]. In 40 patients, inter-observer and intra-observer variability were low (interquartile range of 0–5%). We used the usual CCS risk classification definitions. Low risk was defined as a CCS between 0 and 99, intermediate risk was defined as a CCS between 100 and 399, and high risk was defined as a CCS equal to or greater than 400.

We studied the difference in CCS between the two groups and the relationship between the FRS and the CCS in the stroke group. We also performed univariate and multivariate analyses to identify factors associated with high-risk CCS (CCS $\geq$ 400).

Informed consent for clinical procedures and the research protocol was received from all patients studied. The study was approved by an institutional review board.

Statistical analysis

Data are expressed as mean $\pm$ SD. Continuous laboratory variables were compared using two-group *t*-test. Because the CCS data did not show a normal distribution, the Mann–Whitney test was used to determine differences between the two groups. Discrete variables were expressed as counts or percentages and were compared using the chi-square test or Fisher's exact test. The relationship between a high-risk CCS and patient characteristics was assessed using univariate and multivariate analyses. We performed a multiple logistic regression analysis that included all variables with a value of $p < 0.05$ in the univariate analysis. A *p*-value $<$0.05 was considered statistically significant.

Results

Clinical characteristics of the studied patients are shown in Table 1. Because of the selection criteria, age and the prevalence of male patients were the same in each group. The prevalence of hypertension was significantly higher in the stroke group, while the prevalence of hyperlipidemia, diabetes, smoking, and obesity was not significantly different between the two groups. Laboratory data were also not significantly different between the two groups. Regarding patient medication use, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use were more prevalent in the stroke group. The use of other medications was not significantly different between the two groups.

Fig. 1 shows the CCS of the two groups. The CCS was significantly higher in the stroke group than in the control group (median: 64, interquartile range: 3–382 in the stroke group vs.

Table 1
Clinical characteristics of patients.

	Stroke group $n=151$	Control group $n=151$	*p*
Age (years)	67.3 ± 7.8	67.3 ± 7.8	0.9999
Sex (male)	101 (66.9%)	101 (66.9%)	0.9999
Hypertension	114 (75.5%)	81 (53.6%)	<0.0001
Hyperlipidemia	86 (57.0%)	78 (51.7%)	0.3554
Diabetes	49 (32.5%)	54 (35.8%)	0.5439
Smoking	38 (25.2%)	45 (29.8%)	0.3669
Obesity	30 (19.9%)	35 (23.2%)	0.4839
Laboratory data			
TC (mg/dl)	216.7 ± 46.4	209.8 ± 43.2	0.4515
TG (mg/dl)	147.9 ± 90.6	157.9 ± 96.5	0.5878
HDL-C (mg/dl)	60.7 ± 15.3	61.3 ± 35.8	0.8935
LDL-C (mg/dl)	126.0 ± 39.6	120.2 ± 29.8	0.6706
HbA1c (%)	5.70 ± 0.90	5.72 ± 0.94	0.8743
BS (mg/dl)	131.2 ± 42.1	137.4 ± 41.8	0.6852
Medication			
Aspirin	28 (18.5%)	25 (16.6%)	0.6500
Statin	29 (19.2%)	36 (23.8%)	0.3270
CCB	61 (40.4%)	57 (37.7%)	0.6371
ACE-I/ARB	70 (46.4%)	42 (27.8%)	0.0009
β-Blocker	8 (5.3%)	6 (4.0%)	0.5841
Oral DM agent	21 (13.9%)	30 (19.9%)	0.1669
Insulin	2 (1.3%)	3 (2.0%)	0.6520

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BS, blood sugar; CCB, calcium channel blocker; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

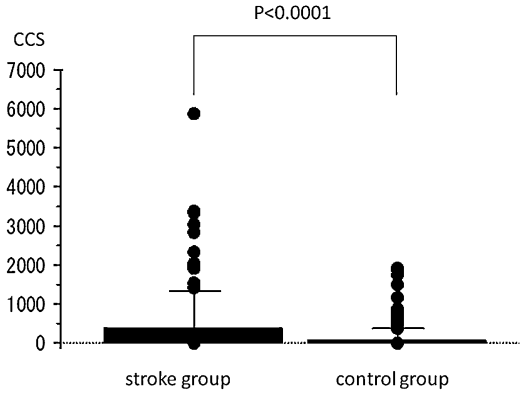

Fig. 1. The coronary artery calcium score of the stroke group and control group. CCS, coronary calcium score.

Table 2
Coronary calcium score in stroke and control group.

	Stroke group $n=151$	Control group $n=151$	p
0	35 (23.2%)	72 (47.7%)	
1–99	50 (33.1%)	48 (31.8%)	
100–399	29 (19.2%)	17 (11.2%)	
400–999	16 (10.6%)	9 (6.0%)	
≥1000	21 (13.9%)	5 (3.3%)	<0.0001

median: 3, interquartile range: 0–65 in the control group, $p < 0.0001$).

Table 2 shows the distribution of CCS in the two groups. Significantly more patients in the stroke group had a higher CCS ($p < 0.0001$). No coronary calcium was detected in 23.2% of the stroke group compared with 47.7% of the control group. High-risk CAD, defined as a CCS ≥ 400, was detected in 24.5% of the stroke group compared with 9.3% of the control group.

Table 3 shows the relationship between FRS and CCS in the stroke group. Among 151 patients in the stroke group, 39, 71, and 41 patients were classified as low, intermediate, and high risk, respectively, according to the FRS. However, risk classification according to CCS showed different results. The CCS identified 82.1% of patients with a low risk FRS as low risk. However, it identified intermediate and high risks in only 19.7% and 39.0% of patients with intermediate and high risk FRS, respectively. Thus, agreement between the FRS and the CCS was found in only 62 patients (41.1%).

Table 3
Framingham risk score and coronary calcium score.

Framingham risk score		Coronary calcium score	
low risk	39 (25.8%)	low risk	32 (82.1%)
		intermediate risk	6 (15.4%)
		high risk	1 (2.5%)
intermediate risk	71 (47.0%)	low risk	37 (52.1%)
		intermediate risk	14 (19.7%)
		high risk	20 (28.2%)
high risk	41 (27.2%)	low risk	16 (39.0%)
		intermediate risk	9 (22.0%)
		high risk	16 (39.0%)

Table 4
The results of univariate analysis associated with high risk coronary calcium score.

	CCS < 400 $n=251$	CCS ≥ 400 $n=51$	p
Age	66.7 ± 7.9	70.1 ± 6.4	0.0043
Sex (male)	158 (62.9%)	44 (86.3%)	0.0013
Hypertension	155 (61.8%)	40 (78.4%)	0.0232
Hyperlipidemia	138 (55.0%)	26 (51.0%)	0.6012
Diabetes	76 (30.3%)	27 (52.9%)	0.0019
Stroke	114 (45.4%)	37 (72.5%)	0.0004
Smoking	65 (25.9%)	18 (35.3%)	0.1705
Obesity	52 (20.7%)	13 (25.5%)	0.4496
Laboratory data			
TC (mg/dl)	214.0 ± 48.5	211.0 ± 42.2	0.7010
TG (mg/dl)	157.2 ± 93.5	161.4 ± 165.1	0.8272
HDL-C (mg/dl)	55.8 ± 15.4	58.0 ± 16.4	0.3985
LDL-C (mg/dl)	128.8 ± 42.2	122.0 ± 30.5	0.3436
HbA1c (%)	6.01 ± 1.37	6.23 ± 1.41	0.3348
BS (mg/dl)	140.2 ± 59.1	140.9 ± 57.1	0.9374

BS, blood sugar; CCS, coronary calcium score; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 5
The results of multiple logistic regression analysis associated with high-risk coronary calcium score.

Variable	OR	95%CI	p
Age	1.09	1.03–1.14	0.001
Diabetes	2.97	1.52–5.78	0.001
Stroke	3.85	1.89–7.81	0.001
Sex (male)	4.41	1.82–10.75	0.001

CI, confidence interval; OR, odds ratio.

Table 4 shows the results of a univariate analysis of factors associated with a high-risk CCS. Age, prevalence of male sex, hypertension, diabetes, and stroke were significantly higher in patients with a CCS ≥ 400 than in those with a CCS < 400. Laboratory data were not significantly different between the two groups. In a multiple logistic regression analysis adjusted for variables associated with a high-risk CCS (CCS ≥ 400), age, diabetes, stroke, and male sex were significantly associated with a high-risk CCS (Table 5).

Discussion

Our results show that the prevalence and severity of CAD were higher in stroke patients without known CAD compared with age- and sex-matched non-stroke patients. Almost 80% of stroke patients had CAD detected by the CCS compared with 50% of non-stroke patients. About a quarter of stroke patients had high-risk CAD (CCS ≥ 400), whereas less than 10% of non-stroke patients had high-risk CAD. Thus, the prevalence of high-risk CAD was more than twofold in stroke patients compared with non-stroke patients. To our knowledge, this is the first study that measured CCS in stroke patients without known CAD and compared it with the CCS of non-stroke patients.

A number of previous studies investigated the prevalence of CAD in stroke patients. Yoo et al. [6] performed coronary computed tomography angiography (CCTA) in 1304 stroke patients. They

found that the frequency of significant (≥50%) CAD and any degree of CAD in this population were 32.3% and 70.1%, respectively. Hoshino et al. [7] studied 104 patients with cerebral infarction. CCTA showed a prevalence of significant CAD of 37.5% in this group. Calvet et al. [8] performed CCTA in 274 patients with non-disabling, non-cardioembolic ischemic stroke or transient ischemic attack and no known CAD. They found significant CAD in 18% of patients. Thus, previous studies have shown that 20–40% of stroke patients have asymptomatic significant CAD.

However, many studies have shown that most cases of myocardial infarction and sudden cardiac death do not arise from the sites of significant coronary narrowing, and that coronary revascularization therapy of coronary obstruction in patients with stable CAD does not reduce the risk of myocardial infarction or cardiac death [16–19]. These observations are explained by the concept of vulnerable plaque, and 70–80% of acute coronary events result from coronary lesions that are not hemodynamically significant or flow limiting before the event [20].

We therefore measured CCS in stroke patients. Coronary artery calcification signifies the presence of coronary atherosclerosis and a strong linear correlation exists between total coronary artery atherosclerotic plaque burden and the extent of coronary artery calcification [21–23]. Coronary artery calcification has been found to be the most powerful predictor of cardiac events, providing independent and incremental information over risk factor-based assessments of asymptomatic patients [9–11]. In 4129 patients from the Heinz Nixdorf Recall study without known CAD, traditional risk factors and CCS were measured [10]. Adding CCS to FRS categories improved the area under curve (AUC) from 0.681 to 0.749 ($p < 0.003$). More recently, in the Multi-Ethnic Study of Atherosclerosis study, 1330 patients with intermediate risk underwent six tests of risk markers (CCS, brachial flow-mediated dilatation, ankle-brachial index, intima–media thickness, family history, and high-sensitivity C-reactive protein) and were followed up for 7.6 years [11]. CCS afforded the highest increment (AUC 0.623 vs. 0.784), while brachial flow-mediated dilatation had the least (0.623 vs. 0.639). Thus, CCS provided superior discrimination and risk reclassification compared with other risk markers. In contrast, patients without detectable calcium have a low rate of coronary death or myocardial infarction over 3–5 years of observation [10,24]. Therefore, the measurement of CCS rather than the detection of significant CAD would be a more rational choice for the risk stratification of asymptomatic CAD in stroke patients. Our results showed that a quarter of stroke patients had high-risk CAD (CCS ≥ 400), which was more than twofold higher than the prevalence in non-stroke patients. In addition, the multivariate analysis showed that age, diabetes, stroke, and male sex were independently associated with high-risk CAD.

Our study also showed that coronary risk score had limited ability for risk stratification. The CCS identified low risk in most of the patients with low risk Framingham scores. However, it identified intermediate and high risks in only 20% and 40% of patients with intermediate- and high-risk Framingham scores, respectively. Agreement between scores was achieved in only 41.1% of them. In about half of the patients with an intermediate risk, Framingham score moved to a low-risk category according to CCS. About 40% of patients with a high-risk Framingham score also moved to a low-risk category. We think this fact has a clinically significant impact on the management of these patients, because these patients do not need further examination, such as CCTA, myocardial perfusion imaging, and coronary angiography, for risk stratification.

Research has revealed the limitations of coronary risk scores. Karim et al. [25] measured subclinical atherosclerosis in 498 healthy subjects, 69% of whom had evidence of subclinical atherosclerosis in more than one of the three vascular beds. Of the 68 subjects with subclinical atherosclerosis in all three vascular beds, only 23% had a high risk FRS. Ahmadi et al. [26] investigated the mortality risk associated with CCS and FRS in 730 subjects classified as low risk versus high risk based on FRS. The mortality rate was 18.5% in the discordant low-risk group (FRS < 10% and CCS > 100), but it was 7.7% in the discordant high-risk group (FRS > 20% and CCS = 0). Therefore, a growing body of evidence supports the fact that global risk scores may be useful guides in predicting long-term cardiovascular disease risk in healthy populations, but are often suboptimal for individual risk estimation [27].

There are several limitations to our study. First, the number of patients was relatively small. To compensate for this limitation, we selected age- and sex-matched non-stroke patients evaluated in the same period and compared these patients with the stroke patients. Second, we excluded patients who had died, patients who had disabling stroke, and patients older than 80 years. Thus, it is likely that because of these exclusions, the CCS of stroke patients was underestimated. Third, CCS is a surrogate for CAD and represents coronary plaque burden, not coronary artery stenosis. In addition, a low CCS does not exclude CAD [28]. Fourth, our study did not include patients with cardioembolic stroke. Cardioembolic stroke can be expected to be associated with a higher likelihood of CAD, probably due to the underlying presence of cardiac disease. One study found significant CAD in 21% of patients with suspected embolic stroke by CCTA, which is similar to that observed in those with non-cardioembolic stroke [29]. We excluded cardioembolic patients because the number of patients was small and many patients had disabling strokes. Fifth, we excluded patients with carotid artery disease because carotid artery disease is already designated as a CHD equivalent. Symptomatic carotid artery disease probably accounts for no more than 10% of patients with ischemic stroke [30].

In conclusion, our study showed that the prevalence of asymptomatic CAD in ischemic stroke patients without known CAD was high, and that a quarter of them had high-risk CAD defined as a CCS ≥ 400. Age, diabetes, stroke, and male sex were independent predictors of high-risk CAD. Thus, these results suggest that the assessment of CAD in asymptomatic ischemic stroke patients is worthwhile.

Conflict of interest

None of the authors have any conflicts of interest.

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